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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/869,668 | 01/02/2002 | Mary F. Fitzgerald | Le A 33 162 | 7045 |

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| EXAMINER | |
|---|---|
| PATEL, SUDHAKER B | |
| ART UNIT | PAPER NUMBER |
| 1624 | |

DATE MAILED: 05/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/869,668 | M.F.Fitzgerald et al |
| **Examiner** | **Art Unit** |
| SUDHAKER PATEL,D.Sc.Tech. | 1624 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Jun 17, 2002*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *1-11, 13, 14, 16, and 17* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-11, 13, 14, 16, and 17* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *2,6*
4) ☒ Interview Summary (PTO-413) Paper No(s). *7*
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Applicants' communication paper # 6 dated 6/17/02 is acknowledged.

Applicants have canceled claims 12,15 in their paper # 5 dated 01/02/2002, and amended claims 1-6,9-11,14,16 and 17.

Claims 1-6 are related to method of use of compounds of ***Formula I***.

Claims 9,10,11 are method of use claims for ***Formula I'***.

Claim 13 recites a condition for a method of treating for claims 1-6,9-11.

Claim 14 recites the respiratory diseases for method claims 1,9,10 or 11.

Claim 17 is a method of treating claim for compounds of claims 7,8.

Claims 7 is related to compounds of ***Formula I'***.

Claim 8 is related to compound of ***Formula I***.

Claim 16 is a pharmaceutical composition claim for compounds of claim 7 or 8.

Therefore, the claims in this application are the claims 1-11,13,14,16,17.

### I. *Election/Restrictions*

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

**Group I**, claim(s) 7,8,16,17,1-4 (in part),5-6,9-11,13-14(in part) drawn to compounds of Formula (I') or Formula (I) wherein A and B are Phenyl; D is carbonyl, corresponding composition and method of use.

**Group II**, claim(s) (in part) 1-4 and 13,14(in part) drawn to a method of use for Formula (T)x A-B-D-E--COOH wherein A,B, and D are other than those of Group I. If this group is elected further restriction/election will be required as there are many unknowns.

2. The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: They have different chemical structures. The claims lack unity of invention because compounds of Formulae I & I' do not possess single structural element that is shared by all of the alternatives. The only common technical feature shared by all of the alternatives of the Formulae I & I', namely a -COOH group, is old. The common structural feature of Formulae I and I', is not a patentable advance over the prior art.

For applicants' quick reference "Unity of Invention rule 37 CFR 1.475" is recited below:

*37 CFR 1.475. Unity of invention before the International Searching Authority, the International Preliminary Examining Authority and during the national stage.*
*(a) An international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ( "requirement of unity of invention "). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features " shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.*

*(b) An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:*
*(1) A product and a process specially adapted for the manufacture of said product; or*
***(2) A product and a process of use of said product;*** *or*
*(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or*
*(4) A process and an apparatus or means specifically designed for carrying out the said process; or*
*(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.*
***© If an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b) of this section, unity of invention might not be present.***
*(d) If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and § 1.476(c).*
*(e) The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.*

Examiner has considered (b) (2) and ( c ) of above guidelines as per rule 37 CFR 1.475 for the restriction/election of this application as stated above.

The claims are drawn to structurally dissimilar compounds which are classified separately, require separate literature searches and are not art recognized equivalents. They are made and used independently.

Note that compounds, corresponding compositions, a method of use and a process of making that are of the ***same scope*** are considered to form a single inventive concept under PCT

Rule 13.1, 37 CFR 1.47(d). The scope that a prior art anticipating one compounds under 35 U.S.C. 102 would not render obvious another compound of the same claim under 35 U.S.C. 103.

3. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

The make up of components (T)xA, B,E, and the various compounds generated by either having substituents or without substituents will represent multiples of species.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

4. The claims are deemed to correspond to the species listed above in the following manner:

*(A).* (T)xA, B, R6 all are aryl;

*(B).* A = pyridine;

(C). A = pyrimidine;

(D). A = pyrazine;

(E). A = pyridazine;

(F). A = pyrrole, oxazole, imidazole, thiazole;

(G). A =Furane, thien, and

The following claim(s) are generic: 1,2,3, 14.

5. The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: They lack unity in the chemical core. The only common variable is the -COOH group.

6. During a telephone conversation with Dr. J. Chiu on 3/5/02 a provisional election was made without traverse to prosecute the invention of Group I, claims 7,8,16,17,1-4 (in part) 5-6,9-11,13-14(in part), and species of working Example 2 as recited on page 83 (= (+)-2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl]-4-(4'-ethoxy[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid). Affirmation of this election must be made by applicant in replying to this Office action.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Applicants have elected invention of Group I with the species of Example 2 as already stated above. Since claims 1-4,13,14 link with other inventions they will be examined bearing in mind the elected subject matter as per invention of Group I and species of Example 2 only.

Applicants are reminded of the election of species guidelines provided in MPEP 803.02, which are followed for examination.

Search was carried out with variables of species for the Formula, "(T)x A-B-D-E--COOH" of generic claim 1 exactly defined as follows:

| | |
|---|---|
| (T)x A | = phenyl; |
| B | =phenyl; |
| D | =-CO-; |
| E | =-CH2-CH(COOH)-alkylene-; |
| R6 | = heterocyle with N i.e. isoindolinone. |

Initial search with above definitions of the variables revealed prior art(s).

As per the guide lines stated above, the examination was limited to compounds of Formula (T)x A-B-D-E--COOH wherein all other than cited above definitions of variables are withdrawn from further consideration.

Therefore, claims 1-4 and 13-14 (all in part) are withdrawn wherein A, B, and D are other than phenyl and carbonyl respectively.37 CFR 1.142(b).

This application has been found to contain more than one invention. Therefore, the requirement for restriction/election is still deemed proper, and is maintained.

## II. *Information Disclosure Statement*

The Information Disclosure Statements submitted as paper # 1 dated 6/29/01, and # 6 dated 6/17/02 are considered by the Examiner and signed copies of PTO Form 1449 are enclosed with this communication for applicants' record.

Preliminary search revealed prior art (WO 9615096 see rejection(s) bellow). Applicants are urged to disclose and provide any related art(s) to this case either of U.S. pending applications or foreign application, because the same will be necessary for consideration prior to allowance.

## III. *Claim Rejections - 35 U.S.C. § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-11,13,14,16,17 are rejected under 35 U.S.C. 102(b) as being anticipated by Kluender et al( WO 9615096 published on 5/22/1996).See Examples 267-273 in Table XX on page 116 wherein the 4'-chloro and 4'-EtO- derivatives of the instant Formula (I) are matching.

The ref. ''096 discloses making of derivatives of substituted 4-biarylbutaric or 5-biarypentanoic acids as MMPs inhibitors and the generalized formula (T)xA-B-D-E-G (see abstract and page 7) as claimed herein.

The meaning of the variables as presented in ref. '096 Examples 267-273 can be related to instant application for the Formula (I) of claim 1(= (T)x A-B-D-E--COOH) as follows:

| | |
|---|---|
| A | = phenyl; |
| (T) | =Chlorine or EtO-; |
| B | =phenyl; |
| D | =-CO-; |
| E | =-CH2-CH(COOH)-alkylene-; |
| R6 | = Bicyclic heterocyle with 1 N i.e. isoindolinone. |

Note, the ref. '096 also teaches making of (+) isomer(s).Additionally, the ref. '096 teaches the utility of the compounds as MMPs inhibitors as claimed herein.

## IV. *Claim Rejections - 35 U.S.C. § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11,13,14,16,17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim.

(A). Claims 1,2 recite a method of treating a respiratory disease with a compound having MMPs activity **and** pharmaceutically acceptable salts **and** prodrugs thereof. Correction to: " **or** pharmaceutically acceptable salts **or** prodrugs thereof" is required.

(B). Claims 1, 2 recite "prodrugs". It is not very clear as to make up of the prodrugs. Applicants do not exactly and definitely recite mode of attachment to atoms involved, the nature of modification, and the number of modification per molecule. The compounds have Nitrogen

atom(s) and a -COOH group. Therefore, the possibilities for N atom are as -N+ - O-,-N-alkyl or N-salt(s), for a -COOH group various esters, amides and amide derivatives. Specification does not provide any guidance.

(C). Independent claims 7,9 recite compounds with a core:" -**COCH2-CH(COOH)-CH2-CH2**-N of Heterocycle in ***pentanone bridge***" which are shown as related Formula (I');

compounds of independent claims 8, 10,11 represent structurally the same core, but are recited as having a:"***oxobutanoic acid bridge***", and

compounds of claim 6 (which is dependent on claims 1,2) does not specifically recite chemical description for the bridge as presented in claims 7,9,10,11.

Compounds of claims 1,2 have generic Formula: (T)x A-B-D-E-COOH.

All of these claims have the same chemical bridge, namely, the structure **-COCH2-CH(COOH)-CH2-CH2**, and therefore, it is not very clear as to what applicants exactly want to present with independent claims 7,8,9, 10, 11 and claim 6 which is dependent on claims 1,2.

(D). Claim 8 has no period at the end. Correction is required.

## *Claim Rejections - 35 U.S.C. § 112*

V. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Method of use claims 1-6,9-11,13,14,17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a disease, does not reasonably provide enablement for "prevention". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Receptor binding is known to be structure sensitive. Note In re Surreey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. See also MPEP2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art. Also note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a), August 2000 edition, which are:

*(1).* The nature of invention;

*(2).* The state of prior art ;

*(3).* The predictability or lack thereof in the art;

*(4).* The amount of direction or guidance present;

*(5).* The presence or absence of working examples;

*(6).* The breadth of the claims, and

*(7).* The quantity of experimentation needed.

**Following references are cited to show the present state of art:**

- Kim et al,:MIliary tuberculosis and acute respiratory distress syndrome", Int. J.Tuberc. Lung Dis. 7/4,359-64 (April 2003), also cited as PubMed Abstract: 12733492.

Kim states that: " ARDS caused by miliary TB is associated with a high fatality rate; ***scope remains for improvement*** in its managenent".

- Rreference (as cited by applicants in IDS) Ricou et al , "MMP and TIMP in ARDS", Am.J.Resp.Crit.Care Med., 154,346-352(1996).
  Ricou states that: " the possibilities of using Matrix Metalloproteinase and TIMP in Acute Respiratory Distress syndrome.( See last paragraph of the article on page 351) and concludes as: " MMP could participate in lung injury in ARDS. High levels of TIMP during the early phases might influence the development of ARDS, whereas 92 G'ase may play a role in the remodeling process of the late phases of the syndrome. A clearer understanding of the respective roles of MMP and TIMP in different clinical stages ***may*** lead to new therapeutic strategies".

Pages 64-78 of the specification describe various assay and test methods used, and specifically on page 76 Table I list IC50 values for MMP-12(nM) for selected 5 compounds, but not for the elected species of Example 2. Note, the results of Table I are for the racemate compounds and not for the purest compounds as claimed herein. Table 3 on page 76 illustrates the selectivity of Examples 4, and 2 for various MMPs. The IC50(nM) values for Example 2 for MMP-3, MMP-8, MMP-13 vary from 3.2 to 70. These results will serve the purpose of preliminary screening only.

There is no demonstration for the ability to prevent diseases as claimed herein by "a process or step of administration of effective amount of a substance or its composition to mammals, such as human, a farm animal or a domestic pet.

This rejection is applied for:

- the level of unpredictability in the art, and
- the direction for prevention of diseases provided as to what other aromatic or heteroaromatic moieties at various locations for A,Q, R2,B,R7 might work.

Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits. The facts provided as above do support the need for additional quantity of experimentation which would be an undue burden to one skilled in the pharmaceutical arts.

**VI.** ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel,D.Sc.Tech. whose telephone number is (703) 308 4709.

The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Dr.Mukund Shah can be reached at (703) 308 4716 or Sr. Examiner Mr. Richard Raymond at (703) 308 4523.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

S.p.

May 18, 2003.

Mukund J. Shah

**MUKUND SHAH**

**SUPERVISORY PATENT EXAMINER**

**ART UNIT 1624**